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Survey on the Ability of Wolbachia to Control Human Viral, Protozoan, and Filarial Disease Pathogens

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Abstract

Objective: Most human filarial nematode parasites and arthropods are hosts for a bacterial endosymbiont, Wolbachia. In filariasis, Wolbachia are required for normal development, fertility, and survival. However, in arthropods, Wolbachia are largely parasitic and can influence development and reproduction, but are generally not required for host survival.

Materials and Methods: Due to their obligate nature in filarial parasites, Wolbachia have been a target for drug discovery initiatives using several approaches including diversity and focused library screening and genomic sequence analysis.

Results: In vitro and in vivo anti-Wolbachia antibiotic treatments have been shown to have adulticidal activity, a long sought goal of filarial parasite drug discovery. In mosquitoes, it has been shown that the presence of Wolbachia can inhibit the transmission of certain viruses, such as dengue, chikungunya, yellow fever, West Nile, as well as the infectivity of the malaria-causing protozoan, Plasmodium and filarial nematodes.

Conclusion: Wolbachia can cause a form of conditional sterility that can be used to suppress populations of mosquitoes and additional medically important insects. Thus, Wolbachia, a pandemic endosymbiont, offers great potential for elimination of a wide-variety of devastating human diseases.

Keywords: Control, Human, Diseases, Wolbachia

Introduction

Most, but not all, species of filarial nematodes contain within their tissues the mutualistic symbiont, Wolbachia, required for fertility, development, and survival, thus providing a novel set of targets for filariasis control. The presence of Wolbachia in arthropods, particularly insects, has also provided the potential means for controlling other insect-borne parasitic diseases, such as malaria and dengue fever.

The development of increasingly rapid, innovative, and sophisticated genomic-related techniques, including NextGen DNA, ribonucleic acid (RNA) and protein sequencing, deoxyribonucleic acid (DNA) capture methods, and associated "dry-lab" bioinformatic analysis methods, has ushered in an exciting age of in-depth analysis of the genomes of Wolbachia and their various invertebrate hosts and studies that seek to unravel their symbiotic interactions (1-3). While only at the beginning stages of this information tsunami, these ever-advancing approaches enable deeper understanding of the roles and effects of Wolbachia on filarial nematode parasitism and vector borne disease, leading to control or elimination of diverse pathogens that together threaten the lives and wellbeing of billions of people.

How Wolbachia controls human viral, protozoan, and filarial disease pathogens

It would be remiss to leave this discussion without mention of the exciting applications of Wolbachia to

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protect human populations from parasitic viral, protozoan, and filarial diseases. In many insects, such as in Drosophila and mosquitoes, the presence of Wolbachia can affect microbial pathogens. This includes affecting the ability of an insect to transmit medically significant pathogens, such as dengue virus, chikungunya virus, yellow fever virus, filarial parasites, and plasmodium protozoans, to humans (4). Mosquitoes of the genera Aedes, Anopheles, and Culex, are the major vectors of human pathogens, including protozoa (Plasmodium sp.) and filariae, and of a variety of viruses (causing dengue, chikungunya, yellow fever, and West Nile). With respect to dengue, the main mosquito vector is Aedes aegypti, but it is not naturally infected with Wolbachia. Different strains of Wolbachia have recently been introduced (Wolbachia strains wMel and wMelPop from Drosophila or wAlbB from A. albopictus) into A aegypti (3,4). Here, dengue virus replication is greatly reduced, lowering the viral risk to the human population.(5).

Transcriptomic studies with follow-up biochemistry have shown that in some mosquitoes, Wolbachia presence correlates with activation of some components of the mosquito immune response. Neither the Toll nor IMD (immune deficiency) pathways are required for the anti-viral effect. Recent reports have shown that Wolbachia confers resistance to the Plasmodium protozoan in Anopheles stephensi, and wAlbB attenuates West Nile virus in Culex quinquefasciatus and reduces filarial parasite viability in A. aegypti. Several Wolbachia strains reduce adult insect life span and may reduce disease transmission of some pathogens because of their long development time in the vector (for example, dengue virus) (6). Therefore, life-shortening Wolbachia might inhibit high titers of the pathogen (7).

Several potential strategies exist for the use of Wolbachia in arthropod based disease control (8,9). These can be divided into two broad categories: Wolbachia population replacements or population reduction. The first strategy contains several possible approaches, all based upon cytoplasmic incompatibility (CI), which can lead to arrested embryonic development in populations that include individuals infected with different Wolbachia types. This phenotype lends itself to manipulation for anti-parasite control. CI was first observed more than 70 years ago but was only linked to Wolbachia within the last 40 years beginning about the time of this journal's first publication (10,11).

One might replace the Wolbachia infection type of the insect vector with one that is more biologically fit and which has anti-parasitic attributes. Here, the Wolbachia infection can reduce disease incidence. It is clear that Wolbachia can invade populations both in cage experiments and in natural populations (12,13). Because the reproductive strategy of arthropod Wolbachia, e.g., CI, ensures its passage to the next generation when artificially or naturally introduced, Wolbachia can be maintained in natural populations even in the presence of negative fitness effects, preventing the infection from being lost. Early work by Curtis and Adak showed that Wolbachia could be driven into natural populations using CI (14). Furthermore, the spread of Wolbachia in previously uninfected natural populations has been well documented (15). For this strategy to be effective, as mentioned previously, the fitness of the novel Wolbachia host must not interfere with its biological propensity. For instance, the mosquito attenuated wMelPop-CLA Wolbachia strain has been shown to reduce the potential for dengue transmission (15). However, this strain shows reduced fitness as the mosquitoes age (16,17). Nevertheless, the further development of such strains may be useful in reduction of human population exposure.

Discussion

A variant approach that also uses Wolbachia replacement would be recombinant genetic transformation of Wolbachia to express a product (for instance a microRNA or protein) in its host that would affect pathogen biology or transmission. Several theoretical transformation approaches have been suggested (17). Despite the inability to grow Wolbachia cells in culture and the lack of robust genetics, recent developments might be of interest. One is the ability to purify Wolbachia, and then put them back into hosts where they are functional (18). Another might use nematode embryos with Wolbachia that can be maintained in culture (18). Brugia, Onchocerca, and D. immitis adults and larval stages can be maintained in culture for a short amount of time. Perhaps the use of Wolbachia phage transduction or Wolbachia secretion systems (i.e., Type IV) might be developed. Modern “genome editing” techniques, such as CRISPER, Zn-finger nucleases, or TALENS, might also be interesting to consider in creating genome mutations in Wolbachia which then can be reintroduced into their respective hosts (19).

Another approach within this strategy might involve the insertion of genes, which could have anti-parasitic effects, into the vector host chromosome or into Wolbachia bacteria along with linked “CI genes” followed by its introduction into a natural population, where it might spread. This, of course, necessitates knowing and being able to manipulate Wolbachia genes responsible for CI, perhaps using genomic methods described above. Modeling suggests this strategy may not be a general solution due to chromosomal versus maternal inheritance patterns. However, this approach has been used for engineering a gene for resistance to T. cruzi into a bacterial symbiont via a shuttle vector (20).

The second general strategy is to reduce insect populations using CI (unidirectional or bi-directional) to create males which, when mated to indigenous females, result in defective embryogenesis. This is a

form of an incompatible insect technique (IIT) using Wolbachia, an offshoot of an older sterile insect technique (SIT) in which repeated introductions of sterile males (created by irradiation or chemical sterilization) are released to mate and reduce population size (20). This also relies on the CI phenotype, through which females are effectively sterilized when they mate with males harboring no or an incompatible Wolbachia strain. Since male mosquitoes do not feed on blood, and thus, do not transmit disease, extensive or repetitive release of male mosquitoes is not a health or nuisance issue. The male Wolbachia phenotype cannot invade the population due to the induced male sterility and strict maternal inheritance. This IIT approach has been used in Burma, where bi-directional CI was successful in reducing a C. quinquefasciatus population (20) Field trials are underway with these approaches with respect to filariasis and dengue and work is underway for the use of IIT against additional insects and diseases, such as malaria and filariasis (21). What makes IIT compelling as a method of reducing insect population is that traditional approaches, such as the use of insecticides, biological control, and larval habitat removal, sometimes fail to affect a substantial proportion of the population, resulting in quick population recovery following treatments. 'Self-delivering' approaches, such as IIT and SIT, have the potential to affect the residual proportion of population that traditional controls fail to reach (22,23).

Conclusion

In summary, recent technical advances from the arthropod and filarial communities provide a set of approaches for parasitic disease control using Wolbachia (24,25). Endosymbiotic bacteria were first observed in insects in the 1920s and similar observations were made in filarial nematodes in the 1970s. The bacteria were subsequently identified as Wolbachia (in the 1930s in mosquitoes and in the 1990s for filaria). These phenomena and description of CI in Culex in the 1970s remained untold for many years (26). As often occurs in science, the linkage of these apparently disparate observations has opened up an intense area of research activity. Over the next several years, advanced application of molecular, biochemical, and cytological techniques will greatly enhance the understanding of the biology and evolution of Wolbachia endosymbionts, and more importantly, enable the application of that knowledge toward human parasitic disease control.

Ethical issues

We have no ethical issues to declare.

Conflict of interests

We declare that we have no conflict of interests.

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